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09/802,110	03/07/2001	James Leushner	VGEN.P-058-2	5580

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EXAMINER	
WILDER, CYNTHIA B	
ART UNIT	PAPER NUMBER
1637	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/22/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	09/802,110	LEUSHNER ET AL.	
	Examiner	Art Unit	
	Cynthia B. Wilder, Ph.D.	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 October 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14-16,18-25 and 27-36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14-16, 18-25 and 27-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment filed 10/12/2006 is acknowledged and has been entered. Claim 14 has been amended. Claims 14-16, 18-25 and 27-36 are pending. All of the arguments have been thoroughly reviewed and considered but are not found persuasive for the reasons discussed below. Any rejection not reiterated in this action has been withdrawn as being obviated by the amendment of the claims. The new grounds of rejections in this Office Action were necessitated by Applicant's amendment of the claims.

This Action is made FINAL.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Previous rejection

3. The claim rejections under 35 USC 102(e) are withdrawn in view of Applicant's amendment. The claim rejections under 35 USC 103(a) are maintained and discussed below.

Claim Rejections - 35 USC § 103

4. Once again, claims 18-19, 23, 24, 30, 31, 35 and 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Digby et al (US 6,432,634) and Ruano (5,427,911, patent date June 27, 1995) in view of Rao (Analytical Biochemistry, vol. 216, pages 1-14, (1994). Regarding claims 18, 19, 23, 24, 30, 31, 35 and 36, Digby et al teach a kit for sequencing a desire gene in a sample, said kit consisting of, in package combination at least one reaction vessel or a plurality of reaction vessels for each of the regions to be sequenced containing a mixture of a plurality of

sequencing primers, one for each gene region to be evaluated. The plurality of sequencing primers each comprising a reactive portion which specifically hybridizes with the DNA in the sample and a label portion, the label portions of the primers being different and distinguishable one from the other. Digby et al further teach wherein kit may further comprise a thermally stable polymerase enzyme, deoxynucleotide triphosphate feedstock, dideoxynucleotide triphosphate and buffer.

Digby et al do not expressly teach wherein the dideoxynucleotide triphosphate is present in a mole ratio to the corresponding deoxynucleotide triphosphate of from 1:50 to 1:1000 or 1:100 to 1:500.

Ruano et al. teach a method for sequencing genomic DNA sample, the method comprising amplifying in vitro with two locus specific primers that flank both ends of the target region to obtain a template, synthesizing simultaneously truncated strands from both ends of the template by introducing a dideoxynucleotide terminator for each of the four bases adenine, guanine, cytosine and thymine and introducing a label or labels specific for either or both of the 5' ends of the synthesizing strands, thermally cycling steps to provide a sufficiently readable signal (col. 2, lines 3-23). Ruano further teaches wherein the dideoxynucleotide triphosphate is in a mole ratio of about 1:10 to the corresponding deoxynucleotide triphosphate (col. 6, lines 47-68).

The reference of Ruano differs from the instant invention in that the reference does not teach wherein the method comprises the dideoxynucleotide triphosphate in a mole ratio of 1:50

to 1: 1000 or in a mole ratio of 1:1000 to 1:500 to the corresponding deoxynucleotide triphosphates.

In a method similar to that of Ruano, Rao teaches a method of direct sequencing of polymerase chain reaction-amplified DNA. Rao teaches wherein the method comprises mixing the PCR-amplified genomic DNA, labeled primer sequencing buffer and Taq polymerase in a tube, adding to the mixture in four separate tubes, four dNTPs and at least one dideoxynucleotide triphosphate, perform thermal cycling (see Table 3, page 5). Rao differs from the instant invention in that Rao does not teach wherein the mole ratio of the ddNTP:dNTP is from 1:50 to 1:1000 or 1:100 to 1:500. Rao also does not teach wherein the polymerase enzyme incorporates dNTPs into an extending nucleic acid polymerase at a rate which is no less than 0.5 times the rate of incorporation of dNTPs. However, Rao discloses that the composition of the dNTP/ddNTP mix varies depending on the type of polymerase preparation used. Rao states that different polymerases require different dNTP/ddNTP ratios for optimal chain terminations and therefore, the reagents or kits for one polymerase cannot be substituted with those for a different polymerase. Rao further teaches that optimal buffer conditions for the synthesizing reaction will vary based on the specific DNA polymerase used (see Table 3 legend). Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the claim invention that the mole ratio of ddNTP to dNTP in the kit of Digby would vary depending on the specific polymerase utilized as taught by Rao. Further, both Digby and Rao teach wherein the polymerase used is THERMOSEQUENASE, which is the same enzyme as used by Applicant.

New Ground(s) of Rejection

THE NEW GROUNDS OF REJECTION WERE NECESSITATED BY APPLICANT'S AMENDMENT OF THE CLAIMS:

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 14-17, 20-22, 27-29, 32-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Digby et al (US 6,432,634 B1, filing date April 18, 1996) in view of Ruano (5,427,911, patent date June 27, 1995). Regarding claims 14-16, 21, 25, 27-28, 33, Digby et al teach a kit for sequencing a specific region from a gene, said kit consisting of, in package combination at least one reaction vessel or a plurality of reaction vessels for each of the regions to be sequenced containing a mixture of a plurality of sequencing primers, one for each gene

region to be evaluated. The plurality of sequencing primers each comprising a reactive portion which specifically hybridizes with the DNA in the sample and a label portion, the label portions of the primers being different and distinguishable one from the other (col. 7, lines 11-20). Digby et al further teach wherein kit may further comprise a thermally stable polymerase enzyme, deoxynucleotide triphosphate feedstock, dideoxynucleotide triphosphate and buffer (col. 3, lines 1-9 and col. 6, lines 58-60). Digby et al teach that the kit and method are useful for evaluating a desired target sequence in a plurality of sample (col. 1, lines 47-54).

Digby et al do not expressly teach wherein a primer specifically binds to the sense strand of said DNA region and a primer specifically binds to the antisense strand of said DNA region and wherein said primers flank one of the DNA regions with the genomic DNA.

Ruano et al. teach a mixture and method for sequencing genomic DNA sample, the method comprising amplifying in vitro with two locus specific primers that flank both ends of the target region to obtain a template, synthesizing simultaneously truncated strands from both ends of the template by introducing a dideoxynucleotide terminator for each of the four bases adenine, guanine, cytosine and thymine and introducing a label or labels specific for either or both of the 5' ends of the synthesizing strands, thermally cycling steps to provide a sufficiently readable signal (col. 2, lines 3-23, See Figure 5). Ruano et al teach wherein one of said specific primers specifically binds to the sense strand and the other primer specifically binds to the antisense strand (col. 12, lines 50-61).

It would have been obvious to one of ordinary skill in the art at the time of the claimed invention to have been motivated to provide primers which specifically binds to the sense strand

of a DNA region and primers which specifically binds to the antisense strand of a DNA region, wherein said primers flank the desired DNA region in a mixture and kit as taught by Digby et al for the benefit of coupling genomic amplification with a process of DNA sequencing via dideoxynucleotide chain termination (col. 1, lines 17-23) as taught by Ruano et al.

Regarding claim 17, 22, 29 and 34, Digby et al teach the kit of claim 14, wherein the kit includes four-deoxynucleotide triphosphate and at least one dideoxynucleotide triphosphate (col. 3, lines 1-9).

Regarding claims 20 and 32, Digby et al teach wherein the kit includes as a non-specific reagent a polymerase enzyme, THERMOSEQUENASE (col. 6, lines 5-7), which is the same polymerase enzyme that Applicant uses in the instant kit. Therefore, the limitation extending nucleic acid polymer at a rate, which is no less than 0.4 times the rate of incorporation of deoxynucleotides, is an inherent property of the polymerase enzyme, THERMOSEQUENASE.

7. ***Applicant's Traversal and Examiner's Response***

Issue I: **Claims 14-17, 20-22, 27-29, 32-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Digby et al (US 6,432,634 B1) in view of Ruano (5,427,911).**

Issue II: **Claims 18-19, 23, 24, 30, 31, 35 and 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Digby et al (US 6,432,634) and Ruano (5,427,911) in view of Rao (Analytical Biochemistry).**

(a) In response to Applicant's remarks and comments, the Examiner acknowledges Applicant's remarks but remind Applicant that the claims are directed to a kit requiring the following elements:

(1) a single reaction vessel containing a mixture of region specific sequencing regents, wherein each region specific sequencing reagents comprises:

--a first primer which specifically binds to the sense strand of a DNA region and flank one of the DNA regions with genomic or microorganism DNA and a detectable label,

--a second primer which specifically binds to the antisense strand of a DNA region which flank one of the DNA region with genomic or microorganism DNA and a detectable label that is different from the label of the first primer,

(2) Optional non-region specific sequencing reagents.

Applicant is reminded that a kit is a product comprising reagents for a desired process. A kit cannot perform any method steps, but only contain reagents that can be used by a practitioner for a desired process. Applicant's claim as currently written reads on any two primers that bind to a sense and antisense strand (e.g., forward and reverse primers for any desired target). The claims further only require detectable and distinguishable labels for each of the primers. The term "specifically binds" in relations to the primer does not provide any structural properties for the primer. Thus, any forward and reverse primer, such as the sense and antisense primers used in polymerase chain amplification reactions are encompassed by the claims as currently written. During methods of performing a PCR reaction, primers for the sense and antisense strands, which flank a desire target, are commonly added in a mixture, prior to thermocycling (see for example, Ruano et al, Figure 5). The limitation "a kit consisting of, in packaged combination" does not provide any structural features of the instant invention, but only

provides a property of the reagents of the kit. The examiner maintains that the cited prior art meets the limitations of the claims as currently amended.

(b) In response to Applicant's arguments that Digby et al do not teach one reaction vessel for each region to be sequenced, instead Digby teach four reaction vessels for each region to be sequenced, it is noted that Digby et al specifically teaches at col. 7, lines 12-20, that "the kit of the invention includes at least one container containing a mixture of a plurality of sequencing primers, one for each gene region to be evaluated. The specification further states that the "plurality of sequencing primers each comprises a reactive portion which hybridizes with DNA in the sample and a label portion, the label portions of the reagents being different and distinguishable one from the other". Therefore, while the Examiner agrees that Digby teaches four reaction vessels, Digby also teaches a single reaction vessel (one container) as noted above.

(c) In response to Applicant's arguments that Digby does not teach binding of the primers to the sense and antisense strands of the DNA in a desired sample, the Examiner agrees that the reference of Digby does not expressly state that the primers are specific for the sense and antisense strands. However, the secondary reference of Ruano expressly teaches this limitation. As noted above, Ruano teaches reagents for amplification coupled with DNA sequencing. Ruano teach a mixture comprising in a single tube, a primer for the sense strand and a primer for the antisense strand along with genomic DNA and dNTPs (see Figure 5 and col. 6, lines 32-38). The obvious benefit of providing both primers in a single mixture is for performing amplification by PCR.

(d) In response to Applicant's arguments that Rao does not meet the limitations of the claims of the instant invention because Rao does not teach the rate of incorporation by the polymerase as claimed and thus the examiner's rejection is based on hindsight reconstruction, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). In this case, contrary to Applicant's argument, the reference teaches the use of the same polymerase as used by Applicant. Rao additionally provides a general teaching as to how the incorporation of dNTPs by a polymerase can differ based on the desired properties of the reaction and polymerase. MPEP states that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the examiner maintains that the reference of Rao provides a suggestion for determining the rate of dNTP incorporation as claimed.

(e) In response to Applicant's arguments that Rao teaches primers that are labeled using the same radiolabel and must therefore be in separate containers, MPEP states that one cannot show nonobviousness by attacking references individually where the rejections are based on

combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In this case, the rejection is based on the combination of Digby in view of Ruano and further in view of Rao. Rao is not cited for its teaching of the primers being labeled with e.g., a fluorescent tag. For this teaching is already taught by Digby (see col. 7, lines 17-19) and Ruano et al (see col. 7, lines 26-59). Rather, Rao is cited for its teaching of parameters of determining the rate of incorporation of dNTPs.

(f) In response to Applicant's arguments that Ruano et al do not meet the limitations of the claims because Ruano teaches a single container, not a single reaction vessel as claimed, it is noted that the instant specification does not provide a limiting definition for "reaction vessel". Additionally, it is noted that the claims are drawn to a kit consisting of, in packaged combination, a single reaction vessel comprising reagents, not an apparatus performing a specific reaction. Therefore, a single container comprising the reagents reads on the instant invention.

(g) In response to Applicant's arguments that Ruano's containers includes a set of instructions which clearly refers to a packaging container, such as a box, not a reaction vessel, since the reaction vessel would obviously not contain a set of instructions, it is noted that the specification does not provide a limiting definition for "the reaction vessel of the kit". Again, Applicant is reminded that the claims are drawn to a "kit", not an apparatus. Contrary to Applicant's argument "a kit" as claimed, would possibly contain a set of instructions for instructing the practitioner how to use the reagents as supplied in the kit in *a packaged* combination.

(g) In response to Applicant's arguments that Ruano et al does not suggest the present invention because the present invention requires that the reagents be mixed in the same reaction vessel, the Examiner asserts that Ruano meets this limitation in the teaching of a tube comprising a mixture of genomic DNA, primers and dNTP (see figure 5). Additionally, it is commonly known that in PCR, the reagents are usually mixed together in a single reaction vessel or tube for thermocycling to occur. In response to Applicant's arguments that the Figure 5 shows that the labeled primers are placed in separate tubes, it is noted that Ruano teaches at col. 6, lines 34-38, that in the Figure 5:

> "[T]he amplified material (template) from tube 10 is split into two aliquots 12. To each aliquot 12, **a labelled primer for each end is added (A' and B').** The label can be a radioactive moiety, a dye or a fluorescent moiety, just to name a few".

(h) In regards to Applicant's arguments concerning "intended use limitations", the Examiner agrees that the Office does not prohibit intended use limitations. However, as stated in the prior Office Action and noted by Applicant, MPEP states that "a recitation of the intended use of the claimed invention must result in a *structural difference* between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim".

Contrary to Applicant's argument, a limitation such as "specifically binds" is not a structural property of the primers, but rather a functional property of the primers. In order to provide a structural property of the primers of the kit, specific sequences of the primer or the target, such as identified by "SEQ ID NO:" would be required and would thus impart

functionality to the kit because it would clearly identify how and/or to what the primers bind for use in sequencing. Applicant's arguments are not sufficient to overcome the prior art rejections noted above.

Conclusion

8. No claims are allowed. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cynthia B. Wilder, Ph.D. whose telephone number is (571) 272-0791. The examiner can normally be reached on a flexible schedule.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Cynthia Wilder

cbw

KENNETH R. HORLICK, PH.D
PRIMARY EXAMINER

1/9/07